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Type III Tracheal Agenesis With Familial Tetralogy of Fallot and Absent Pulmonary Value Syndrome

Kerri Hirt-Armon, Barbara R. Pober, and Lewis B. Holmes

Department of Newborn Medicine, Brigham and Women's Hospital, Boston (K.H.-A., L.B.H.); Department of Human Genetics, Yale University, New Haven (B.R.P.), Connecticut; and Genetics and Teratology Unit, Massachusetts General Hospital, Boston (L.B.H.), Massachusetts

We describe a female infant born at 33 weeks gestation diagnosed postnatally with a previously unreported phenotype consisting of Type III tracheal agenesis plus tetralogy of Fallot with absent pulmonary valve. She was delivered to a mother who had the same congenital heart malformation, but no detectable tracheal abnormality. We discuss possible etiologies of these malformations.

KEY WORDS: tracheal agenesis (TA), tetralogy of Fallot (TOF), congenital absence of pulmonary valve syndrome (CAPV), ventricular septal defect (VSD), fluorescent in situ hybridization (FISH)

INTRODUCTION

Since the first case of tracheal agenesis was documented in 1900 [Payne], well over 60 additional cases have been reported. To date, it has been impossible to investigate the hereditary nature of tracheal agenesis, as this sporadic malformation is almost always fatal. While absence of the trachea can occur as an isolated malformation, some 84% of reported cases are associated with other anomalies, most often with heart defects [Manschot et al., 1994]. Most infants with tracheal agenesis are born prematurely from a pregnancy associated with maternal polyhydramnios. At birth, the neonate generally presents with respiratory distress and is incapable of producing an audible cry, despite great effort. In this report, we discuss a female infant born with a previously unreported phenotype of Type III tracheal agenesis with familial tetralogy of Fallot and absence of the pulmonary valve.

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Address reprint requests to Dr. Lewis B. Holmes, Genetics and Teratology Unit, Massachusetts General Hospital, Warren Building, Rm 801, 32 Fruit Street, Boston, MA 02114-2696.

CLINICAL HISTORY

Pregnancy was uneventful until the 14th week, when spotting occurred. Ultrasonography detected the presence of partial placenta previa. Fetal echo-cardiography performed at 20 weeks to rule out structural heart defects was inconclusive. Sonography at 30.6 weeks showed severe polyhydramnios and a "double bubble" in the fetal abdomen, suggesting duodenal atresia. The mother was started on a daily regimen of ferrous gluconate and folic acid around the 6th week of pregnancy and had one urinary tract infection in the 11th week for which Ampicillin was prescribed. There was no exposure to known teratogenic agents.

This 1,445 g female child was delivered limp with no cry by cesarean section to a 31-year-old G2P0 woman at 33 weeks gestation. The Apgar scores at 1 and 5 minutes were 1 and 5, respectively. Following delivery, the infant was noted to be in respiratory distress. Tracheal intubation was attempted and proved difficult. Under high ventilatory pressures, the infant's heart rate increased and her status improved. She was transferred to the neonatal intensive care nursery where she experienced cyanotic and bradycardiac episodes. Attempts to pass an endotracheal tube were unsuccessful secondary to the presence of a stenotic larynx. Esophageal intubation was carried out, and the patient improved with ventilation.

Fluoroscopic examination of the esophagus and airway indicated absence of the trachea. By cardiac ultrasonography, a large ventricular septal defect and abnormalpulmonary valve were identified. Postnatal abdominal radiograph confirmed the presence of the "double bubble," which was assumed to be secondary to duodenal atresia. Based on the severity of the defects identified, the medical team and the parents concluded that no further treatment was possible. The infant died 7 hours after birth.

An autopsy confirmed absence of the trachea just below the true vocal cords. The right and left mainstem bronchi were attached to the distal esophagus. Tetralogy of Fallot with extreme hypoplasia and dysplasia of pulmonary valve, and marked dilation of main and left pulmonary arteries were found. There was also an annular pancreas causing duodenal dilation, and an aberrant right subclavian artery arising from the descend-

ing aorta distal to the left subclavian artery. Bilateral clinodactyly of the fifth finger was the only anomaly noted on surface examination. The only histologic abnormalities detected were restricted to the liver. Histologic studies identified hepatic fibrosis. The infant's liver showed striking bile ductular proliferation, cholestasis, portal fibrosis, excessive extramedullary hematopoiesis, increased hepatocellular iron, iron in ductular epithelium, and lesser Kupffer cell iron. There was no evidence of necrosis, inflammation, or giant cell formation.

Chromosome study by amniocentesis identified no abnormality in the proposita. Studies performed on blood samples collected from the parents also failed to detect chromosomal abnormalities in either the mother or the father.

Family History

The 31- and 37-year-old Caucasian mother and father are non- consanguineous. The mother had been admitted to Boston's Children's Hospital at 6 months of age with respiratory distress. Cardiac catheterization showed the presence of a ventricular septal defect (VSD) and narrowing of the pulmonary artery valve. Dilation of the right pulmonary artery, causing secondary obstruction of the right main stem bronchus, which in turn induced obstructive emphysema, was also noted by cardiac catheterization.

At age 21, the mother was recatheterized and was found to have tetralogy of Fallot, absence of the pulmonary valve with pulmonary regurgitation, aneurysmal dilation of main and right pulmonary arteries, and a patent foramen ovale for which she subsequently underwent surgical repair.

Recently, we evaluated the mother for a chromosome 22 microdeletion found in the DiGeorge/Velocardiofacial syndromes by use of the fluorescent in situ hybridization (FISH) technique. No deletion was found. Pulmonary function tests were also performed on the mother. There was no evidence of tracheal obstruction either on in- or expiration. In addition, the mother has never had a history of liver dysfunction.

Aside from the mother and daughter, there are no other relatives with tetralogy of Fallot with absent pulmonary valve, or any other heart defect. A niece of the mother was born with a cleft palate, but no other malformations have been identified in either family.

DISCUSSION

Floyd et al. [1962] delineated three forms of tracheal agenesis: Type I is partial atresia with a normal short segment of distal trachea arising from the anterior esophageal wall; Type II is complete tracheal agenesis, with normal bronchi, bifurcation, and carina and the latter connecting to the esophagus; and Type III is complete agenesis of the trachea with the bronchi originating directly from the esophagus. The infant we report had Type III.

Tracheal agenesis (TA) is almost always a fatal malformation. Definitive repair of this anomaly requires a tracheal prosthetic, which has yet to be developed [Faro et al, 1979]. While previous attempts at surgical repair were unsuccessful [Floyd et al., 1962; Fonkalsrud et al., 1963], recently a case of Type II TA with proximal tracheoesophageal and bronchoesophageal fistulas was managed successfully [Hiyama et al., 1994].

The cause of TA remains unknown. By the end of the 3rd week, a rudimentary respiratory system begins to develop from a diverticulum on the foregut caudal to the pharyngeal pouches. By the 6th week, two longitudinal esophagotracheal ridges develop on each side of the diverticulum and eventually fuse to form a septum. Until recently, it was presumed that the trachea and lungs arise from the ventral portion and the esophagus from the dorsal portion [Sadler, 1979]. On this basis, it has been proposed that TA is due to ventral displacement of the tracheoesophageal septum [Bremer, 1957].

In a study of human embryos, Zaw-Tun [1982] found that the trachea develops from a ventral outgrowth off the foregut, but did not find evidence that the trachea separates from the esophagus via an ascending septum. Kluth et al. [1987], in their study of chick embryos, cast further doubt on the existence of a septum in the division of the foregut. Their findings suggested that a reduction in the size of the primitive foregut, caused by a system of folds that grow close together, but do not actually fuse, leads to the development of the esophagus and trachea. On the basis of their findings, they proposed that tracheal atresia with fistula may result from a ventral deformation of the foregut. A dorsal displacement of the tracheoesophageal space occurs when the developmental movements of the folds are disturbed. It is this space that differentiates into the esophagus. In this case, a dilated PA, which impinges on the trachea, may be yet an additional factor that led to the poor development of this child's trachea.

Evans et al. [1985] reported that patients with TA had a pattern of associated anomalies including complex congenital heart disease, duodenal and laryngeal atresia, VSD, aberrant lung lobation, and gastric, splenic, and pancreatic anomalies. Our patient had many of the common TA-associated malformations noted by Evans et al. In their review of 31 patients with tracheal agenesis, 77.4% had congenital heart defects. Although 6.5% of the 31 patients reviewed by Evans et al. had tetralogy of Fallot (TOF), none had TOF with congenital absence of the pulmonary valve (CAPV) [Evans et al., 1985].

The combination of VSD and CAPV, documented in our patient and her mother, is a rare form of TOF. Findings in CAPV range from complete absence of the pulmonary valve to the presence at the annular level of nubbins of embryonic tissue [Reginato et al., 1982]. Our infant's condition was consistent with the latter, in that only a few fibrous nodules were present around the pulmonary valve ring. The heart in the proposita had a single, large VSD located in the bifurcation of the septal band, a finding usually seen in cases of TOF with CAPV [Emmanouilides et al., 1989]. Although a right aortic arch is common, our infant had a normal, left aortic arch. The ductus arteriosus is almost always absent and is consistent with the findings in our infant. Dilation of the proximal PA, which was found in this infant on autopsy, frequently leads to compression of the tracheobronchial tree [Zuberbuhler, 1989].

Familial cases of TOF with CAPV have been documented. Friedberg [1974] reported tetralogy in a man, his daughter, her child, and a cousin and suggested that the pattern of transmission was most consistent with autosomal dominant inheritance. The cardiac anomaly in child and cousin included CAPV. In their report of two sisters born to first cousin parents with tetralogy and pulmonary valve atresia, Der Kaloustian et al. [1985] suggested that this may be a unique manifestation of TOF inherited as an autosomal recessive disorder. In addition to a different mode of inheritance, the family we report most likely represents a more distinct form of TOF with CAPV than the family described by Der Kaloustian et al.

Although TOF has been associated with TA [Evans et al., 1985] and with CAPV [Reginato et al., 1982; Der Kaloustian et al., 1985; Friedberg, 1974], the combination of TOF, CAPV, and TA has not, to our knowledge, been reported before. A review of the literature did not show any other cases of familial congenital heart disease in infants with agenesis of the trachea.

While congenital hepatic fibrosis has been linked with congenital heart disease [Naveh et al., 1980], it has not heretofore been associated with TA. In a review of the literature, the only liver anomalies noted in infants with TA were an additional anterior-superior liver lobe [Raso, 1993] and "minor form anomalies of the liver and spleen," [Effmann et al., 1975]. The liver pathology in this case does not appear to be secondary to extra-hepatic biliary obstruction, infantile polycystic disease, infection, congenital heart disease, or to alpha-1-antitrypsin deficiency. Hence, the cause of the fibrosis remains unclear.

Though an undetected chromosome microdeletion cannot be ruled out, we think it is more likely that the mother has a less severe form of the same malformation-complex present in her daughter. The genetic basis for these malformations is likely to be due to either multifactorial or autosomal dominant inheritance.

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